

## Facial selectivity in the reaction of dihalocarbenes with 2-substituted 4,7-dihydro-1,3-dioxepines

Vitaly Yu. Fedorenko, Rustam N. Baryshnikov, Rusalina M. Vafina,  
Yurii G. Shtyrlin and Evgenii N. Klimovitskii\*

A. M. Butlerov Chemical Institute, Kazan State University, 420111 Kazan, Russian Federation.  
Fax: +7 843 292 7278; e-mail: evgenii.klimovitskii@ksu.ru

DOI: 10.1016/j.mencom.2007.05.013

The dichloro(dibromo)cyclopropanation of conformationally heterogeneous 2-substituted 4,7-dihydro-1,3-dioxepines was found to afford a low selectivity; *endo* addition on the side of a remote alkyl substituent is governed by the  $\pi$ -facial solvation of substrates.

The inspection of electronic, steric and solvation terms controlling  $\pi$ -facial selectivity is of great theoretical and commercial interest in organic chemistry due to diverse reactions at the  $sp^2$  reactive centre. The role of the conformational properties of substrates in the formation of the stereochemical outcome is poorly known.<sup>1,2</sup> Conformationally heterogeneous 2-substituted 4,7-dihydro-1,3-dioxepines **1a–d** are suitable objects in [4 + 2] cycloaddition reactions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate<sup>3,4</sup> and hexachlorocyclopentadiene.<sup>5</sup> The substrates exist in solution as an equilibrium of the forms with different spacial architectures: chair with equatorial alkyl and twist-boat conformations. For acetals **1a–c**, the twist-boat form dominates (4:1), whereas for **1d** the ratio is found to be inverted.<sup>3,6</sup> According to Curtin–Hammett/Winstein–Holness concepts, the overall kinetic description of such reactions leading to cross products is complicated and the stereochemical outcome appeared to be a function of four reaction rate constants and the ground state conformational population.<sup>7</sup> Note that the chair conformation has  $C_s$  symmetry but the twist-boat one belongs to the  $C_2$  point group. Both *endo* and *exo* approaches to the double bond of the twist-boat form are practically equal for an incoming reagent. The stereodefined environment of the double bond in the chair conformation dictates the *exo* face to be more accessible. Thus, the symmetry arguments render the stereochemical course of reactions with the participation of chair and twist-boat forms quite different. The stereochemical results of the Diels–Alder reaction above<sup>3,4</sup> revealed that  $\pi$ -facial selectivity was exclusively

**Table 1** Reaction conditions of dihalocarbene cycloaddition to 2-substituted 4,7-dihydro-1,3-dioxepines and *endo*-isomers **2** and **3**, fraction (%).<sup>a</sup>

R	CHCl <sub>3</sub> / 50% NaOH/ BTEAC <sup>b</sup>	CHBr <sub>3</sub> / 50% NaOH/ BTEAC	CCl <sub>3</sub> COOEt/ MeONa	Decomposition of CCl <sub>3</sub> COONa <sup>c</sup>
Me	54	55	—	—
Et	53	56	55	54
Pr <sup>i</sup>	54	55	—	—
Bu <sup>t</sup>	57	58	60	—

<sup>a</sup>The accuracy is  $\pm 3$ . <sup>b</sup>Increasing the temperature from 298 up to 333 K did not change the product ratio. <sup>c</sup>In pentane and CHCl<sub>3</sub>.

sensitive to the conformational equilibrium constant, the bulk of the remote substituent and, finally, the solvent effect. It seems reasonable to clarify the peculiarities of seven-membered unsaturated acetals **1a–d** in the reactions with dichloro(dibromo)-carbenes (Scheme 1). According to modern concepts, a low selectivity of dihalocyclopropanation reactions is surely a reflection of both a low activation energy and earlier transition state.<sup>8,9</sup>

Several methods were applied in carbene generation.<sup>10</sup> We have used the two-phase Makosza method for CCl<sub>2</sub> (CBr<sub>2</sub>)<sup>†</sup> formation; ethyl<sup>‡</sup> and sodium<sup>§</sup> trichloroacetates served as a source of CCl<sub>2</sub>. The results are collected in Table 1.

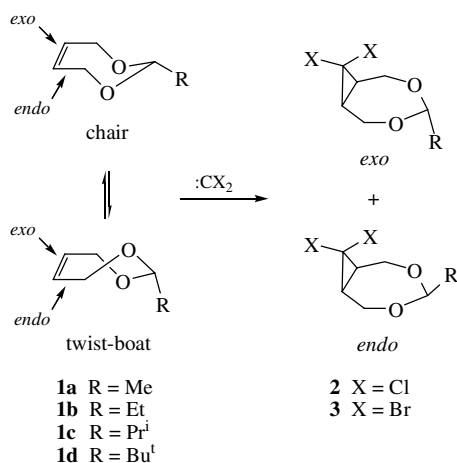
The Makosza procedure gave the highest yields (50–70%) of the products. Under ultrasonic irradiation, reaction times were

<sup>†</sup> A 50% solution containing 7 g of NaOH was added to a solution of 43.5 mmol of the corresponding 2-substituted 4,7-dihydro-1,3-dioxepine and 0.3 g (1 mmol) of benzyltriethylammonium chloride (BTEAC) in 28 ml of CHCl<sub>3</sub> at 278 K for 2 h. The reaction mixture was stirred for 50 h at room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. The organic layer was separated and dried over Na<sub>2</sub>SO<sub>4</sub>.

Dibromocarbene formation procedure is similar, and 30.5 ml of CHBr<sub>3</sub> was used. A UZDN-A device with a frequency of 20 kHz was used for ultrasonic activation.

<sup>‡</sup> 10 g (52.2 mmol) of ethyl trichloroacetate was added to the suspension of 7.3 g (135.2 mmol) of sodium methoxide and 46 mmol of 2-substituted 4,7-dihydro-1,3-dioxepine in 25 ml of pentane with stirring at 270 K for 15 min. The reaction mixture was stirred for 8 h at room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. The organic layer was separated and dried over Na<sub>2</sub>SO<sub>4</sub>; the unreacted starting material was evaporated. The same procedure was applied to the reaction in CHCl<sub>3</sub>.

<sup>§</sup> The mixture of 3 g (23.4 mmol) of 2-ethyl-4,7-dihydro-1,3-dioxepine, 24.5 g (132.2 mmol) of sodium trichloroacetate and 0.5 g (1.6 mmol) of BTEAC in 30 ml of CHCl<sub>3</sub> was stirred at 333 K for 7 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. The organic layer was separated and dried over Na<sub>2</sub>SO<sub>4</sub>, and the unreacted starting material was evaporated.



Scheme 1